EXHIBIT A

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/885,259	02/23/2001	Madhav N. Devalaraja	PC18174A	3713

7590 04/07/2004

Paul H. Ginsburg
Pfizer Inc
Patent Department
235 E. 42nd Street (150-05-49)
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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/885,259	DEVALARAJA ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12, 14 , 31, 33-34, 36-37, 39, 41-42 and 44 - 50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12, 14 , 31, 33-34, 36-37, 39, 41-42 and 44 - 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/28/04 has been entered.

Claims 12, 14 , 31, 33-34, 36-37, 39, 41-42 and 44 - 50 are pending.

In view of the amendment, filed 6/12/02(Paper No. 13), the following rejection remains

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 12, 14 , 31, 33-34, 36-37, 39, 41-42 and 44 - 50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: 1) a method for screening for an inhibitors of a CSF and M-CSF in *in vitro* assays based on inhibition of chemoattraction and/or accumulation and /or activation of leukocytes by CSF and; 2) *in vivo* recruitment assay response to IL-8, using rabbit as animal model, does not reasonably provide **enablement** for: 1) a method of treating inflammation, such as sepsis, or osteoporosis, an autoimmune disease or atherosclerosis, comprising administering to a mammal a therapeutically effective amount of an antibody to M-CSF, claimed in Claims 12 and 14, or 2) a method of treating inflammation, such as psoriasis or asthma, comprising administering to a mammal a therapeutically effective amount of an antibody to M-CSF, claimed in Claims 31, 37 and 42 or 3) a method of treating rheumatoid arthritis in a mammal comprising administering an antibody to M-CSF, claimed in Claims 34 and 50. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action, Paper No: 10, mailed 07/28/03

Applicant's arguments, filed 01/28/04 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) the claims, as amended are sufficiently enabled under 35 U.S.C. 112, first paragraph and cited references by Campbell et at , wherein administration of an anti-M-

CSF antibody in a mouse CIA model reduced the severity of established CIA and Williams et al. wherein andimistering of anti-TNFα monoclonal antibody results in reduction in mouse CIA model.

Contrary to Applicant's assertion, the issue raised in the previous Office Action was that the specification does not adequately teach how to effectively treat inflammation, including sepsis, osteoporosis, autoimmune disease, atherosclerosis, rheumatoid arthritis, asthma and psoriasis, by administering an effective amount of an antibody to M-CSF. Moreover, no animals were used as model system to effectively treat inflammation, such as sepsis, or osteoporosis, an autoimmune disease or atherosclerosis, or psoriasis, or asthma, or rheumatoid arthritis comprising administering to a mammal a therapeutically effective amount of an antibody to M-CSF. Since there is no animal model system in the specification to effectively treat inflammation, including sepsis, osteoporosis, autoimmune disease, atherosclerosis, rheumatoid arthritis, asthma and psoriasis, by administering to a mammal a therapeutically effective amount of an antibody to M-CSF, it is unpredictable how to correlate *in vitro* results with *in vivo* use. The references provided by Applicant , for example Williams et al. only teach the use of neutralizing anti-TNF-alpha monoclonal antibody to ameliorate arthritis in mice model with type II collagen –induced arthritis. However, Williams et al., stressed that conformation of the importance of possible modes of therapy and treatment in humans can only come from studies from the amelioration of human rheumatoid arthritis (see page 9788 in particular) . Similarly, Campbell et al. only teach that administration of an anti-M-CSF antibody in a mouse CIA model. However, Campbell et al. teach that little know whether endogenous M-CSF is required for disease development and further that caution should be taken in administering treatment to arthritis patients (see pages 144 and 149 in particular). Moreover, in the other publication Campbell et al. (J. of Immunol. 1998, , v.1998, pages 3639-3644) teach that the approaches that used the inhibitors of a CSF or receptor antagonists of the cytokines to develop the methods of treating inflammation have several limitations such as: 1) the inhibitors of CSF, including monoclonal antibody may not be accessible to the site of the action; 2) there may be reduced efficacy of the neutralizing antibody due to an immune response to this foreign protein (see Discussion overlapping pages 3642-3643 in particular). Mestas et al (J. of Immunology, 2004, 172, pages 2731-238) teach that there exist significant differences between mice and humans in immune system development, activating and response to challenge in both the innate and adaptive arms. As therapies for human diseases become ever more sophisticated and specifically targeted it becomes increasing important to understand the potential limitations of extrapolating data from mice to humans. The literature is littered with the examples of therapies that work well in mice but fail to provide similar efficacy in humans. Feldman et al. (IDS) teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease, leading to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". Feldman et al . further teach that in a chronic immune-driven inflammatory response there are a number of pathways that become engaged and effective therapy in immune inflammatory diseases such as rheumatoid arthritis, will come from therapy aimed at several points in the disease pathway. Aoki et al (US Patent 5,470,578) teach that the cause of a chronic multiple inflammatory disease,

rheumatoid arthritis, is still unknown and no reliable treatment of the disease has been established (see entire document, column 1, lines 55-60 in particular). Since the method of treating inflammation, by administering to a mammal a therapeutically effective amount of an antibody to M-CSF can be species- and model-dependent (seeVan Noort et al. International Review of Cytology, 1998, v.178, pages 127-204, Table III in particular) , it is not clear that reliance on the *in vitro* studies accurately reflects the relative mammal and human efficacy of the claimed therapeutic strategy. The specification does not teach how to extrapolate data obtained from *in vitro* studies to the development of effective *in vivo* mammalian including human therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of a method of treating inflammation, including sepsis, osteoporosis, autoimmune disease, atherosclerosis, rheumatoid arthritis, asthma and psoriasis by administering to a mammal a therapeutically effective amount of an antibody to M-CSF . Moreover, Applicant himself acknowledge that the ability of CSF to synergistically enhance the chemoattractant effects of chemokines on recruitment of leukocytes to sites of inflammation was unexpected (page 4, line 8 of the Specification as filed) . As such, the invention must be considered unpredictable.

The specification does not provide sufficient teaching as to how it can be assessed that treating inflammation in a subject, including sepsis, rheumatoid arthritis, asthma and psoriasis was achieved after the administration of a therapeutically effective amount of an antibody to M-CSF Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of treating inflammation in a subject, including sepsis, rheumatoid arthritis, asthma and psoriasis, comprising administering an effective amount of a therapeutically effective amount of an antibody to M-CSF in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

3. No claim is allowed

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
April 5, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

PC18174A

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

APPLICANT :	M. DEVALARAJA, ET AL.	EXAMINER : M. BELYAVSKYI
SERIAL NO:	09/885,259	ART UNIT : 1644
FILED:	FEBRUARY 23, 2001	PAPER NO :
FOR:	INHIBITORS OF COLONY STIMULATING FACTORS	

AMENDMENT

Commissioner for Patents
PO BOX 1450
Alexandria, Virginia 22313-1450

Dear Sir:.

In response to the Office Action mailed April 7, 2004, Applicants respectfully request reconsideration of the above-identified application in view of the following remarks and amendments. A petition to extend the time for response to the Office Action for three months, from July 7, 2003 to October 7, 2004 is being submitted concurrently herewith. In the event that one is not, applicants hereby make such petition and authorize the office to charge deposit account 23-0455 the required amount, or any amount required for additional extension of time.

Amendments to the Claims are reflected in the listing of the claims which begin on page 2 of this paper.

Remarks begin on page 3 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-33. (canceled).

34. (currently amended): A method of treating rheumatoid arthritis in a mammal comprising administering to said mammal ~~an~~ a therapeutically effective amount of an antibody to a M-CSF that is effective to treat said rheumatoid arthritis.

35. (canceled).

36. (previously presented): The method of claim 34 wherein said antibody is a monoclonal antibody.

37-47. (canceled):

48. (previously presented) The method of claim 34, wherein said M-CSF is a human M-CSF.

49. (previously presented) The method of claim 36, wherein said M-CSF is a human M-CSF.

50. (currently amended) A method of treating rheumatoid arthritis in a mammal comprising administering to said mammal ~~an~~ a therapeutically effective amount of an antibody to a human M-CSF that is effective to treat said rheumatoid arthritis.

51. (new) A method of treating rheumatoid arthritis in a human comprising administering to said human a therapeutically effective amount of a monoclonal antibody to a human M-CSF that is effective to treat said rheumatoid arthritis.

52. (new) A method of treating rheumatoid arthritis in a human comprising administering to said human a therapeutically effective amount of a monoclonal antibody to a M-CSF.

REMARKS

STATUS OF THE CLAIMS

Claims 12, 14, 31, 33-34, 36-37, 39, 41-42, and 44-50 were pending in the application. Claims 34 and 50 have been amended. Claims 51 and 52 have been added. Claims 12, 14, 31, 33, 37, 39, 41, 42, 44, 45, 46 and 47 have been canceled. Claims 34, 36, and 48-52 would be pending in the application if the instant amendment is entered. Applicants believe no new matter is added by the instant amendments.

Applicants thank Examiners Chan and Belyavskyi for extending the courtesy of the telephonic interview conducted with the Applicant's representative Eric J. Baude on August 11, 2004, wherein the enablement rejection was discussed. No agreement was reached on the claims. The amendment of the claims to rheumatoid arthritis was discussed and as well as providing in vivo animal data.

I. REJECTION UNDER FIRST PARAGRAPH OF 35 U.S.C. § 112

The Examiner has rejected claims 12, 14, 33-34, 36-37, 39, 41-42, and 44-50 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled for 1) a method of treating inflammation, such as sepsis, or osteoporosis, an autoimmune disease, or atherosclerosis, comprising administering to a mammal a therapeutically effective amount of an antibody to M-CSF, claimed in Claims 12 and 14; 2) a method of treating inflammation, such as psoriasis or asthma, comprising administering to a mammal a therapeutically effective amount of an antibody to M-CSF, claimed in Claims 31, 37 and 42; or 3) a method of treating rheumatoid arthritis in a mammal comprising administering an antibody to M-CSF, claimed in Claims 34 and 50.

Applicants respectfully maintain that claims 34, 36, and 48-52 are sufficiently enabled under 35 USC § 112, first paragraph. Claims 12, 14, 31, 33, 37, 39, 41, 42, 44, 45, 46 and 47 have been canceled and therefore the enablement rejection is rendered moot as to those claims. Claims 34, 36, and 48-52 are directed towards methods of treating rheumatoid arthritis. The specification discloses that M-CSF antibodies, including monoclonal antibodies, are useful as therapeutic agents in the treatment of rheumatoid arthritis (see e.g., page 15, lines 1-12). The Mobley declaration is being

submitted herewith under 37 C.F.R. § 1.132 to demonstrate the effectiveness of polyclonal and monoclonal M-CSF antibodies in treating rheumatoid arthritis. The Collagen Monoclonal Antibody-Induced Arthritis assay in mice is described in the Mobley declaration as being recognized in the art as being reasonably correlated to rheumatoid arthritis in humans (see Mobley declaration ¶13). The Collagen Monoclonal Antibody-Induced Arthritis assay was known to those of skill in the art at the time the present application (filed February 23, 2001) and the provisional patent application to which priority is claimed was filed (March 20, 2000 - United States Serial No. 60/190,842) (see Mobley declaration ¶¶9-11). In a murine Collagen Monoclonal Antibody-Induced Arthritis assay, administration of a goat anti-mouse M-CSF polyclonal antibody was able to reduce paw swelling (see Mobley declaration ¶¶15-25). In addition, the administration of anti-M-CSF monoclonal antibodies after the induction of arthritis was also able to decrease paw swelling in the Collagen Monoclonal Antibody-Induced Arthritis assay (see Mobley declaration ¶¶26-45). Accordingly, the Mobley declaration demonstrates that the administration of an M-CSF antibody was able to ameliorate arthritis in mice in a model that reasonably correlates to rheumatoid arthritis. Therefore, Applicants maintain that the specification enables one of skill in the art to make and use the claimed invention. Accordingly, Applicants respectfully request that the enablement rejection under 35 U.S.C. § 112 be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at 734-622-2095.

Respectfully submitted,

Dated: September 15, 2004

Eric J. Baude
Registration No. 47,413
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105
Telephone: (734) 622-2095
Facsimile: (734) 622-1553

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

APPLICANT :	M. DEVALARAJA, ET AL.	EXAMINER : M. BELYAVSKYI
SERIAL NO:	09/885,259	ART UNIT : 1644
FILED:	FEBRUARY 23, 2001	PAPER NO :
FOR:	INHIBITORS OF COLONY STIMULATING FACTORS	

DECLARATION OF JAMES L. MOBLEY UNDER 37 C.F.R. § 1.132

I, James L. Mobley, do hereby make the following declarations:

1. I am an Associate Research Fellow in the Inflammation Pharmacology Department of Pfizer Global Research and Development at 2800 Plymouth Road, Ann Arbor, MI, 48105.

2. I have been employed as a pharmacologist at Pfizer Inc. and a company acquired by Pfizer Inc., Warner-Lambert Inc., since 1997.

3. In 1984, I earned my B.S. from the University of Illinois, Urbana-Champaign in Biology.

4. In 1987, I earned my M.S. from the University of Illinois, Urbana-Champaign in Biology.

5. In 1991, I earned my Ph.D. from the University of Iowa, Iowa City in Immunology.

6. A copy of my curriculum vitae is attached as Exhibit A.

7. I have read the contents of the Office Action in 09/885,259 and in particular the Examiner's rejection of claims 12, 14, 33-34, 36-37, 39, 41-42, and 44-50 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled.

8. The Collagen Monoclonal Antibody-Induced Arthritis assay is a mouse model of rheumatoid arthritis which involves injecting a cocktail of monoclonal antibodies to type II collagen epitopes into a mouse to induce arthritis.

9. The Collagen Monoclonal Antibody-Induced Arthritis assay was known to those of skill in the art at least since 1995 as evidenced by the publication of Terato et al. (1992) *J. Immunol.* 148: 2103-2108 and Terato et al. (1995) *Autoimmunity* 22(3):137-147.

10. The present application (filed February 23, 2001) claims priority to a provisional patent application filed on filed March 20, 2000 - United States Serial No. 60/190,842.

11. Therefore, Terato et al. (1992), Terato et al. (1995), and the Collagen Monoclonal Antibody-Induced Arthritis assay were in the public domain at the time provisional application and the present application were filed.

12. The Collagen Monoclonal Antibody-Induced Arthritis assay is commonly carried out under my supervision in my laboratory to assess the effects of compounds for their activity as rheumatoid arthritis therapeutics.

13. In my opinion, the murine Collagen Monoclonal Antibody-Induced Arthritis model reasonably correlates to human rheumatoid arthritis.

14. The following three experiments, Experiments 1, 2, and 3, were carried out under my supervision to test anti-M-CSF antibodies in the Collagen Monoclonal Antibody-Induced Arthritis assay in mice.

Experiment #1

15. Twelve Balb/c female mice, 6-8 weeks old, were divided into three groups of four animals each - Group A, Group B, and Group C.

16. A cocktail of four type II collagen epitope antibodies, Arthrogen-CIA® Monoclonal Antibody Cocktail, is commercially available for use in the Collagen Monoclonal Antibody-Induced Arthritis model from CHEMICON International, Inc., Temecula, CA.

17. On day 0 of the experiment, each of the mice in all of the groups were injected intra-peritoneally with 400 µl (4 mg) of Arthrogen-CIA® Monoclonal Antibody Cocktail to induce arthritis.

18. On day 1 post-Arthrogen-CIA® Monoclonal Antibody Cocktail administration the mice were injected intra-peritoneally with 400 µl of phosphate-buffered saline containing 50 µg of the respective antibody for that group:

    Group A - normal goat IgG Control (R&D Systems Inc., Minneapolis, MN, Catalog number Cat # AB-108-C);

    Group B - polyclonal goat anti-mouse TNF-α antibody (R&D Systems Inc., Minneapolis, MN, Catalog number AF-410-NA); and

    Group C - polyclonal goat anti-mouse M-CSF antibody (R&D Systems Inc., Minneapolis, MN, Catalog number AB-416-NA).

19. On day 2 post-Arthrogen-CIA® Monoclonal Antibody Cocktail administration each of the mice was injected intra-peritoneally with 200 µl lipopolysaccharide (LPS) (250 µg/ml; derived from E. coli strain 0111B4).

20. On day 4 post-Arthrogen-CIA® Monoclonal Antibody Cocktail administration the respective groups were injected intra-peritoneally with 400 µl of phosphate-buffered saline containing 50 µg of the respective antibody for that group:

    Group A - normal goat IgG Control (R&D Systems Inc., Minneapolis, MN, Catalog number Cat # AB-108-C);

    Group B - polyclonal goat anti-mouse TNF-α antibody (R&D Systems Inc., Minneapolis, MN, Catalog number AF-410-NA); and

Group C - polyclonal goat anti-mouse M-CSF antibody (R&D Systems Inc., Minneapolis, MN, Catalog number AB-416-NA).

21. All of the groups were assayed for paw swelling using a Dyer Digital Caliper (#655-030-4916) on days 0, 2, 5, 8, 10, and 12.

22. A Change score is the sum of the differences between the width (in millimeters) of all four paws and the two rear ankles of a mouse on day 0 and the width of all four paws and the two rear ankles of that same mouse on a later day in the experiment (e.g., day 2, day 5, day 8, day 10 and day 12).

23. The mean change score ± the standard error of the mean for each group versus the day post-Arthrogen-CIA® Monoclonal Antibody Cocktail administration is graphed in Exhibit B (attached).

24. The mean change score for the M-CSF antibody treated group (Group C) is lower than the mean change score for the control normal goat IgG antibody treated group (Group A) for days 8 and 10 (see Exhibit B).

25. The lower mean change score of the polyclonal M-CSF antibody AB-416-NA treated group (Group C) as compared to the control normal IgG antibody treated group (Group A) for days 8 and 10 indicates that the M-CSF antibody administration is able to decrease the severity of the Collagen Monoclonal Antibody-Induced Arthritis.

Experiment #2

26. Twenty female Balb/c mice, 6-8 weeks old, were divided into 5 groups of four animals each - Group D, Group E, Group F, Group G, and Group H.

27. On day 0 of the experiment, each of the mice in all of the groups were injected intra-peritoneally with 400 µl (4 mg) of Arthrogen-CIA® Monoclonal Antibody Cocktail to induce arthritis.

28. On day 1 post-Arthrogen-CIA® Monoclonal Antibody Cocktail administration the respective groups were injected intra-peritoneally with:

Group D - phosphate-buffered saline (PBS);

Group E - mouse anti-mouse M-CSF monoclonal antibody 2A9.B9 (1 mg);

Group F - mouse anti-mouse M-CSF monoclonal antibody 2C2.B10 (1 mg);

Group G - mouse anti-mouse M-CSF monoclonal antibody 3C4.C9 (1 mg); and

Group H - mouse anti-mouse M-CSF monoclonal antibody 4D8.D6 (500 μg).

29. The mouse anti-mouse M-CSF monoclonal antibodies, 2A9.B9; 2C2.B10; 3C4.C9; and 4D8.D6 were isolated from hybridomas generated by Green Mountain Inc. (Burlington, VT). The hybridomas were obtained using standard hybridoma technology from M-CSF null mice that had been injected with mouse M-CSF.

30. On day 2 post-Arthrogen-CIA® Monoclonal Antibody Cocktail administration each of the mice was injected intra-peritoneally with 100 μl LPS (250 μg/ml; derived from E. coli strain 0111B4).

31. All of the groups were assayed for paw swelling using a Dyer Digital Caliper (#655-030-4916) on days 0, 2, 4, 7, 9, and 11 to generate a mean change score as described above in ¶22.

32. The mean change score ± the standard error of the mean for each group versus the day post-Arthrogen-CIA® Monoclonal Antibody Cocktail administration is graphed in Exhibit C (attached).

33. On Days 4, 7 and 9, Group E (monoclonal antibody 2A9.B9 (1 mg dose)) exhibited a lower mean change score as compared to the PBS control group (Group D).

34. On Days 4, 7, 9 and 11, Group F (monoclonal antibody 2C2.B10 (1 mg dose)) exhibited a lower mean change score as compared to the PBS control group (Group D).

35. On Day 4, Group G (monoclonal antibody 3C4.C9 (1 mg dose)) exhibited a lower mean change score as compared to the PBS control group (Group D).

36. On Days 4, Group H (monoclonal antibody 4D8.D6 (500 μg dose)) exhibited a lower mean change score as compared to the PBS control group (Group D).

Experiment #3

37. Fifteen 6-8 weeks old female Balb/c mice were divided into 3 groups: Group I, Group J, and Group K.

38. Seven days prior to Arthrogen-CIA® Monoclonal Antibody Cocktail administration and 1 day prior to Arthrogen-CIA® Monoclonal Antibody Cocktail administration, the Group J mice were each injected intra-peritoneally with 100 μg of rat anti-mouse M-CSF monoclonal antibody (R&D Systems Inc., Minneapolis, MN, Catalog number MAB416).

39. One hour prior to Arthrogen-CIA® Monoclonal Antibody Cocktail administration the Group K mice were each injected intra-peritoneally with 100 μg of MAB416.

40. On day 0 of the experiment, each of the mice in all of the groups were injected intra-peritoneally with 400 μl (4 mg) of Arthrogen-CIA® Monoclonal Antibody Cocktail to induce arthritis.

41. On day 2 post-Arthrogen-CIA® Monoclonal Antibody Cocktail administration each of the mice was injected intra-peritoneally with 100 μl LPS (250 μg/ml; derived from E. coli strain 0111B4).

42. All of the groups were assayed for paw swelling using a Dyer Digital Caliper (#655-030-4916) on days 0, 2, 4, 7, 9, 11, and 14 to generate a mean change score as described above in ¶22.

43. The mean change score ± the standard error of the mean for each group versus the day post-Arthrogen-CIA® Monoclonal Antibody Cocktail administration is graphed in Exhibit D (attached).

44. On Days 7, 9, and 11 the Group K mice which were administered monoclonal antibody MAB416 (100 µg dose) one hour prior to Arthrogen-CIA® Monoclonal Antibody Cocktail administration exhibited a lower mean change score as compared to the mice of Group I.

45. The Group J mice which were administered monoclonal antibody MAB416 (100 µg dose) 7 days and 1 day prior to Arthrogen-CIA® Monoclonal Antibody Cocktail administration did not exhibit a lower mean change score as compared to the mice of Group I.

CONCLUSION

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: September 14, 2004

By: _____

James L. Mobley

Exhibit A

CURRICULUM VITAE

James L. Mobley

Pfizer Global Research and Development
2800 Plymouth Road
Ann Arbor, MI 48105

EDUCATION

Ph.D.	Immunology University of Iowa, Iowa City December, 1991
M.S.	Biology (GPA 3.92/4.00) University of Illinois, Urbana-Champaign May, 1987
B.S.	Biology (GPA 3.83/4.00) University of Illinois, Urbana-Champaign May, 1984
A.S.	Wabash Valley College, Mt. Carmel, IL May, 1982 GPA 3.93/4.00

POSTGRADUATE TRAINING

Intramural NIH Postdoctoral Training Grant Fellowship, Department of Pathology, The University of Iowa College of Medicine, Iowa City, IA, 1992.

Cancer Research Institute Postdoctoral Fellowship, Department of Microbiology and Immunology, The University of Michigan School of Medicine, Ann Arbor MI/The University of Minnesota Dept. of Lab Medicine and Pathology, Minneapolis, MN, from 1992 to 1995 under the direction of Dr. Yoji Shimizu.

Post-doctoral Research Scientist, Cell Biology and Inflammation Research Unit, Pharmacia & Upjohn, Inc., Kalamazoo, MI, 11/6/95 to 4/11/97.

POSITIONS HELD

Associate Research Fellow, Inflammation Pharmacology, Pfizer Global R & D, 2002-present
Research Associate, Inflammation Therapeutics, PGRD, 2000-2002
Senior Scientist, Immunopathology, Parke-Davis Pharmaceutical Research, 1997-2000

HONORS and AWARDS

Phi Theta Kappa Honor Society, 1982
Phi Kappa Phi Honor Society, 1983
Outstanding Student Award, Wabash Valley College, 1982
Student Senate President, Wabash Valley College, 1982
Illinois Eastern Community College School Board, student representative,1982
Microbiology Graduate Student Organization, president, 1990

PROFESSIONAL AFFILIATIONS

American Association for the Advancement of Science
American Association of Immunologists
Ad hoc reviewer for the Journal of Immunology

INVITED PROFESSIONAL DUTIES

Workshop Chairman, "Lymphocyte Trafficking and Adhesion", Autumn Immunology Conference, Chicago, IL, 1997.

Block Symposium Co-chairman, "Inflammation and Inflammatory Diseases", Federation of American Societies for Experimental Biology meeting, Washington D.C, 1999.

Symposium Chairman, "Pattern Recognition Receptors in Inflammation", Autumn Immunology conference/Inflammation Research Association, Chicago, 2003.

Symposium Co-chairman, "Innate Immunity", Inflammation Research Association International Conference, Lake George, NY 2004.

GRANTS AWARDED

Cancer Research Institute Postdoctoral Fellowship "Intracellular requirements for activation-dependent regulation of VLA integrin function" 1/1/93-10/31/95

Arthritis Foundation Postdoctoral Fellowship, 1993. Declined in favor of Cancer Research Institute Fellowship

The Irvington Institute for Medical Research Postdoctoral Fellowship, 1993.Declined in favor of Cancer Research Institute Fellowship

NIH Public Health Service Postdoctoral Fellowship, 1993. Declined in favor of Cancer Research Institute Fellowship.

TEACHING EXPERIENCE

Teaching Assistant, Introduction to Immunology (G&D 307), The University of Illinois 1985-87. Duties included preparation and presentation of a lecture/discussion on basic immunology to upper level undergraduates and graduate students.

Teaching Assistant, General Microbiology Lab, The University of Iowa, 1987-1991. Duties included overseeing an introductory microbiology lab course 4 hours/day, 2 days/week, 1 semester/year. Students included Medical, Dental, Physician Asst. and Nursing students.

THESES DIRECTED

James T. Wise, M.S. (Eastern Michigan University) - Adoptive transfer of allergic lung inflammation in mice.

PUBLICATIONS

1. Mobley, J. L., and M. O. Dailey. 1991. Regulation of adhesion molecule expression by antigen-specific T cells in vivo. In *Lymphatic Tissues and In Vivo Immune Responses*. B. A. Imhoff, S. Berrih-Aknin, and E. Ezine, eds. Marcel Dekker, Inc., New York, NY, pp. 915-920.

2. Mobley, J. L., and M. O. Dailey. 1992. Regulation of adhesion molecule expression by CD8 T cells in vivo. I. Differential regulation of $gp90^{MEL-14}$ (LECAM-1), Pgp-1, LFA-1, and VLA-4α during the differentiation of cytotoxic T lymphocytes induced by allografts. *J. Immunol.* 148: 2348-2356.

3. Mobley, J., G. Evans, M. O. Dailey, and S. Perlman. 1992. Immune response to a murine Coronavirus:Identification of a homing receptor-negative CD4 T cell subset that responds to viral glycoproteins. *Virology* 187: 443-452.

4. Mobley, J. L., S. Rigby, and M. O. Dailey. 1994. Regulation of adhesion molecule expression by CD8 T cells in vivo. II. Expression of L-selectin (CD62L) by memory cytolytic T cells responding to minor histocompatibility antigens. *J. Immunol.* 153: 5443-5452.

5. Mobley, J. L., P. J. Reynolds, and Y. Shimizu. 1993. Regulatory mechanisms underlying T cell integrin receptor function. *Seminars in Immunology* 5: 227-236.

6. Shimizu, Y., and J. L. Mobley. 1993. Distinct divalent cation requirements for integrin

mediated CD4 T lymphocyte adhesion to ICAM-1, fibronectin, VCAM-1, and invasin. *J. Immunol.* 151: 4106-4115.

7. Reynolds, P. J., J. L. Mobley, and Y. Shimizu. 1993. Lymphocytes and extracellular matrix. In *Lymphocyte Adhesion Molecules*. Y. Shimizu ed. R. G. Landes Company, Austin, TX.

8. Mobley, J. L., E. Ennis, and Y. Shimizu. 1994. Differential activation-dependent regulation of integrin function in cultured human T leukemic cell lines. *Blood* 83: 1039-1050.

9. Mobley, J. L. and Y. Shimizu. 1994. Measurement of cellular adhesion under static conditions. In *Current Protocols in Immunology*, J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, and W. Strober, eds. Greene Publishing Associates, New York, NY, (Unit 7.28).

10. Mobley, J. L., N. C. Romzek, and Y. Shimizu. 1996. Integrin activation in lymphocyte adhesion. In *Handbook of Experimental Immunology*, Blackwell Scientific Publications, Cambridge, (Chapter 68).

11. Mobley, J. L. E. Ennis, and Y. Shimizu. 1996. Isolation and characterization of cell lines with genetically distinct mutations downstream of protein kinase C that result in defective activation-dependent regulation of T cell integrin function. *J. Immunol.* 156: 948-956.

12. Shimizu, Y., J. L. Mobley, L. D. Finkelstein, and A. S. H. Chan. 1996. A role for phosphatidylinositol 3-kinase in the regulation of β1 integrin activity by the CD2 antigen. *J. Cell Biol.* 131: 1867-1880.

13. Zell, T., S. W. Hunt III, J. L. Mobley, L. D. Finkelstein, and Y. Shimizu. 1996. CD28 mediated upregulation of β1 integrin adhesion involves phosphatidylinositol 3-kinase. *J. Immunol.* 156: 883-886.

14. Mobley, J. L., J. E. Chin, and I. M. Richards. 1996. Glucocorticoids, old and new: biological function and use in the treatment of asthma. *Expert Opinion on Investigational Drugs* 5: 871-884.

15. Mobley, J. L., J. E. Chin, and I. M. Richards. 1997.Cytokine networks in allergic lung inflammation. *Expert Opinion on Investigational Drugs* 6:1-6.

16. Hatfield, C. A., J. R. Brashler, G. E. Winterrowd, F. P. Bell, R. L. Griffin, S. F. Fidler, K. P. Kolbassa, K. L. Shull, J. L. Mobley, I. M. Richards, and J. E. Chin. 1997. Intercellular adhesion molecule-1 deficient mice have antibody responses but impaired leukocyte recruitment. *Am. J. Physiol.* 273: L513-L523.

17. Chan, A. S. H., J. L. Mobley, G. B. Fields, and Y. Shimizu. 1997. CD7-mediated regulation of integrin adhesiveness on resting human T cells involves tyrosine phosphorylation-dependent activation of phosphatidylinositol 3-kinase. *J. Immunol.* 159: 934-942.

18. Kivens, W. J., S. W. Hunt III, J. L. Mobley, T. Zell, C. L. Dell, B. E. Bierer, and Y. Shimizu. 1998. Identification of a proline-rich sequence in the CD2 cytoplasmic domain critical for regulation of integrin-mediated adhesion and activation of phosphatidylinositol 3-kinase. *Mol. Cell. Biol.* 18: 5291-5307.

19. Chen, C., J. L. Mobley, O. Dwir, F. Shimron, Vgrabovosky, R. R. Lobb, Y. Shimizu, and R. A. Alon. 1999. High affinity VLA-4 subsets expressed on T cells are mandatory for spontaneous adhesion strengthening but not for rolling on VCAM-1 in shear flow. *J. Immunol.* 162: 1084-1095.

20. Wise, J. T., T. J. Baginski, and J. L. Mobley. 1999. An adoptive transfer model of allergic lung inflammation in mice is mediated by $CD4^+CD62L^{low}CD25^+$ T cells. *J. Immunol.* 162: 5592-5600.

21. Bullard, D. C., J. L. Mobley, L. A. Hurley, J. M. Justen, L. M. Sly, J. G. Chosay, C. J. Dunn, J. R. Lindsey, A. L. Beaudet, and N. D. Staite. 1999. Acceleration and increased severity of collagen-induced arthritis in P-selectin deficient mice. *J. Immunol.* 163: 2844-2849.

22. Mobley, J.L. 2004. Is rheumatoid arthritis a consequence of natural selection for enhanced tuberculosis resistance? *Medical Hypotheses* 62:839-843.

PATENTS

1. U.S. Patent No. 6,696,440 - Treatment of asthma with MEK inhibitors.

ABSTRACTS and PRESENTATIONS

1. Mobley, J. L., and M. O. Dailey. Down-regulation of homing receptor expression on CTL activated in vivo. Abstract published and presented at a poster session at the Federation of American Societies for Experimental Biology meeting, Atlanta, GA. 1990.

2. Mobley, J. L., and M. O. Dailey. Adhesion molecule expression identifies the state of differentiation of CD8 T cells. Abstract published and presented at a poster session at the Federation of American Societies for Experimental Biology meeting, New Orleans, LA. 1991.

3. Dailey, M. O., M. Comito, and J. L. Mobley. Regulation of adhesion molecule expression

during the activation and differentiation of T cells in vivo. Abstract published and presented at a poster session at the Federation of American Societies for Experimental Biology meeting, New Orleans, LA. 1991.

4. Mobley, J. L., S. M. Rigby, and M. O. Dailey. Adhesion molecule expression on effector and memory CD8 T cellls in vivo. Abstract published and presented at a poster session at the Federation of American Societies for Experimental Biology meeting, Anaheim, CA. 1992.

5. Mobley, J. L., S. M. Rigby, and M. O. Dailey. L-selectin expression by memory cytotoxic T cells in vivo. Abstract presented at the 8th International Congress of Immunology, Budapest, Hungary, 1992.

6. Mobley, J. L. and Y. Shimizu. Differential activation-dependent regulation of integrin function in cultured human T cell lines. Poster presented at the Gordon Research Conference on Cell Contact and Adhesion, Andover, NH. 1993.

7. Mobley, J. L., E. Ennis, and Y. Shimizu. A mutational analysis of the activation dependent regulation of human T cell integrin function. Poster presented at the Midwest Autumn Immunology Conference, Chicago, IL. 1994.

8. Mobley, J. L. and Y. Shimizu. CD2-mediated activation of MAP kinase is dependent on phosphatidylinositol 3-kinase function. Poster presented at the Midwest Autumn Immunology Conference, Chicago, IL. 1995.

9. Mobley, J. L., C. A. Hatfield, K. P. Kolbasa, I. M. Richards, and J. E. Chin. Inhibition of antigen-induced murine lung inflammation by peritonitis induction concurrent with immunization. Presented at The American Thoracic Society meeting, San Fransisco, CA. 1997.

10. Mobley, J. L., C. A. Hatfield, J. R. Brashler, S. F. Fidler, I. M. Richards, and J. E. Chin. Elevated Th2-mediated immune response to inhaled antigen in mice genetically deficient in P-selectin expression. Presented at The American Thoracic Society meeting, San Fransisco, CA. 1997.

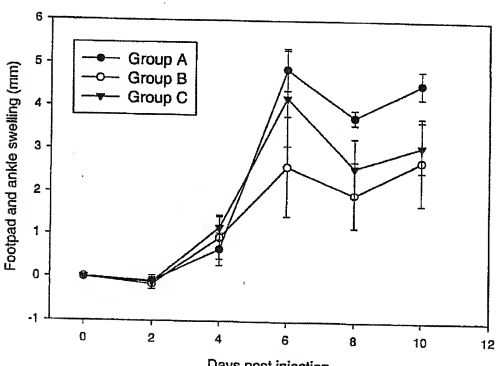
11. Mobley, J. L., J. T. Wise, T. J. Baginski, and M. R. Raynor. An adoptive transfer model of allergic lung inflammation in mice is mediated by $CD4^{+}CD62L^{low}CD25^{+}$ T cells. Presented at the Federation of American Societies for Experimental Biology meeting, Washington D.C, 1999.

12. Gilbertsen, R. B., K. P. Chan, C. A. Vento, T. J. Baginski, M. Raynor, H. Tecle, D. Dudley, and J. L. Mobley. Potent inhibition of T cell activation and cytokine production by the MEK inhibitor PD 184352: Efficacy in a murine asthma model following continuous dosing.

Keystone symposium on T cell stimulation, activation, and death. 2000.

13. Spencer, N. F. L., M. Raynor, and J. L. Mobley. Subset-specific migration of CD4 T cells into the lungs of ovalbumin-challenged mice. Presented at the Federation of American Societies for Experimental Biology meeting, Washington D.C, 2000.

Exhibit B



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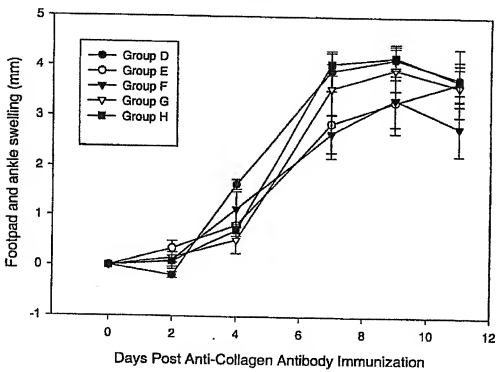
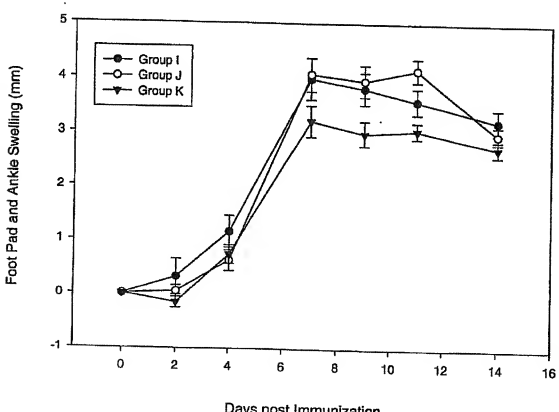


Exhibit D



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/885,259	02/23/2001	Madhav N. Devalaraja	PC18174A	3713

28880 7590 11/22/2004

WARNER-LAMBERT COMPANY
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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/885,259	DEVALARAJA ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34, 36, 48 -52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34, 36, 48 -52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 09/15/04 is acknowledged.

Claims 34, 36, 48 -52 are pending and under consideration in the instant application.

2. The rejection of claims 12, 14, 31,33-34,36-37,39, 41-42,and 44-50, now claims 34,36 and 48-52 under 35 U.S.C. 112, first paragraph is here by withdrawn in view of Applicant's amendment filed 09/15/04 in conjunction with Declaration of Dr. Mobley under 37 C.F.R 1.132. Said declaration provided evidences that polyclonal and monoclonal M-CSF antibody were effective to ameliorate arthritis in collagen monoclonal antibody-induced arthritis assay in mice.

The New Ground of Rejections are set forth herein.

3 . The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 34, 36, 48 -52 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 5,837,460.

US Patent '460 teaches a method for ameliorating the effects of inflammation including rheumatoid arthritis in a mammal , comprising administering to said mammal a therapeutically effective amount of an antibody to M-CSF including human M-CSF (see entire document, Abstract and columns 5 and 9 in particular). US Patent '460 teaches that antibody is monoclonal antibody (see overlapping columns 5 and 6 in particular)

The reference teaching anticipates the claimed invention.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 34, 36, 48 -52 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/09561 in view of Campbell et al (IDS).

WO'561 teaches a method for ameliorating the effects of inflammation in a subject including rheumatoid arthritis, comprising administering an antibodies against GM-CSF, (see entire document, Abstract and overlapping pages 6-7 in particular). WO'561 teaches that). WO'561 teaches that said antibody is monoclonal antibody or humanized antibody (see page 6 in particular).

WO'561 does not explicitly teach a method for ameliorating the effects of inflammation in a subject including rheumatoid arthritis, comprising administering an antibodies against M-CSF

Campbell et al., teach that colony- stimulating factors (CSF) are a family of four cytokine growth factors including macrophage CSF (M-CSF) and granulocyte-marcophage CSF (GM-CSF) each known to exhibit certain activities that predispose them towards a proinflammatory role *in vivo*.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Campbell et al to those of WO' 561 to obtain a claimed method for treating rheumatoid arthritis in a mammal comprising administering an antibody to a M-CSF

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because colony- stimulating factors (CSF) are a family of four cytokine growth factors including macrophage CSF (M-CSF) and granulocyte-marcophage CSF (GM-CSF) each known to exhibit certain activities that predispose them towards a proinflammatory role *in vivo* as taught by Campbell et al. Thus the antibody to one member of the family, i.e. GM-SCF can be substituted with antibody to the other member of the family, i.e. M-CSF in the method of treating rheumatoid arthritis in patients taught by WO 00/09561.

The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
November 15, 2004

Christina Chan

***.